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FRIEDEL-CRAFTS REACTION WITH FURAN

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

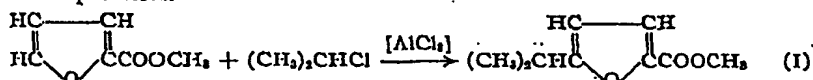
Super-Aromatic Properties of Furan. II. The Friedel-Crafts Reaction

BY HENRY GILMAN AND N. O. CALLOWAY

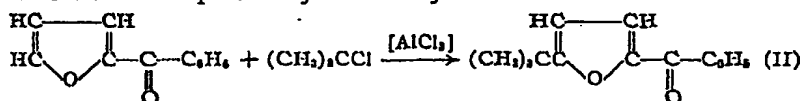
Introduction

The scission of furylphenyllead and furylthienyllead compounds by hydrogen chloride has been presented as evidence in support of the super-aromatic nature of furan.¹ In a by-and-large definition of aromatic compounds and aromatic properties,² the Friedel-Crafts reaction is important historically as one of a small number of transformations peculiarly characteristic of aromatic compounds.³ We now know that this reaction is shown not only by unsaturated aliphatic compounds, but also apparently by some saturated aliphatic compounds.⁴ However, the reaction is still considered, in the aggregate, as a transformation that is typical of aromatic compounds.

Not all aromatic compounds undergo the Friedel-Crafts reaction. This is particularly true of many benzenoid types having a meta-orienting substituent. One of the most striking illustrations is nitrobenzene, which finds application as a solvent or medium for some Friedel-Crafts reactions. Not only do furan and 2-methylfuran undergo acylation,⁴ but we have found that some so-called negatively substituted furans also participate in Friedel-Crafts reactions. Methyl 2-furoate, for example, undergoes ready alkylation and acylation under customary conditions, and the related methyl benzoate does not show these reactions. Substitution takes place in the α -position.



The same type of condensation occurs with 2-furoic acid and with 2-furyl phenyl ketone. The reaction with 2-furyl phenyl ketone is particularly significant because it presents an opportunity to observe the relative aromaticities of a 2-furyl and a phenyl nucleus in a symmetrical compound. Condensation takes place only in the furyl nucleus.



(1) Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932).

(2) Victor Meyer, "Die Thiophengruppe," Brunswick, 1888, p. 276.

(3) Krapivina, *Bull. Soc. Imp. Nat. Moscou*, **1**, 176 (1908); v. Braun and Kuhn, *Ber.*, **45**, 1267 (1912), and **60**, 2557 (1927); Norris and Couch, *This Journal*, **42**, 2320 (1920); Wieland and Bettay, *Ber.*, **55**, 2940 (1922); Nenitzescu and Ionescu, *Ann.*, **491**, 180 (1931); Hopff, *Ber.*, **64**, 2730 (1931), and **65**, 482 (1932); Unger, *ibid.*, **65**, 407 (1932).

(4) Reichstein, *Helv. Chim. Acta*, **13**, 350 (1930).

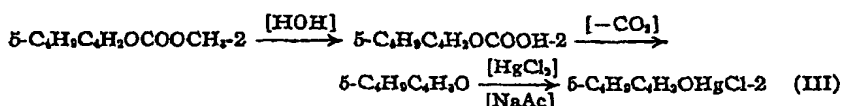
This preferential nuclear substitution, and the condensations with methyl furoate but not with methyl benzoate, together with the fact that benzene can be used as a medium for some Friedel-Crafts reactions of furan are advanced as supporting evidence for the concept that furan has superaromatic properties.

As previously mentioned,¹ some benzenoid types are apparently more aromatic than others. This is especially true of benzene derivatives having amino and phenolic or substituted amino and substituted phenolic⁴ groups. In accordance with this general principle it has been found that methyl anisate (*p*-CH₃OC₆H₄COOCH₃), unlike methyl benzoate, undergoes the Friedel-Crafts reaction. Also, the correlation of the α -positions in naphthalene with the α -positions in furan⁵ finds support in the observation that the Friedel-Crafts reaction takes place with ethyl α -naphthoate.

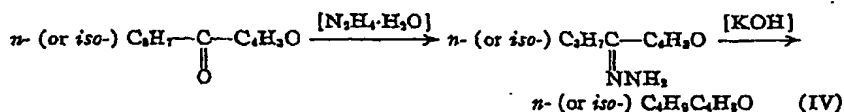
Constitution of Products.—The structure of 5-*tert*-butyl-2-furyl phenyl ketone was established by comparison with the product obtained by interaction of 5-*tert*-butyl-2-furoyl chloride with benzene and aluminum chloride.

The ketones obtained from furan and acid chlorides were identical with those prepared from 2-furylmercuric chloride and the acid halides, and from 2-furonitrile and the appropriate Grignard reagent.⁶

The alkylation products of methyl 2-furoate were somewhat unusual in the sense that the alkyl group appeared to undergo rearrangement so that, for example, each of the four butyl chlorides (as well as butylene) gave some of the same product: namely, methyl 5-*tert*-butyl-2-furoate. The structure of this compound was established by a process of exclusion. The *n*-butyl-, isobutyl-, and *sec*-butyl derivatives were synthesized and shown to be unlike the compound obtained by the Friedel-Crafts reaction which was characterized as follows



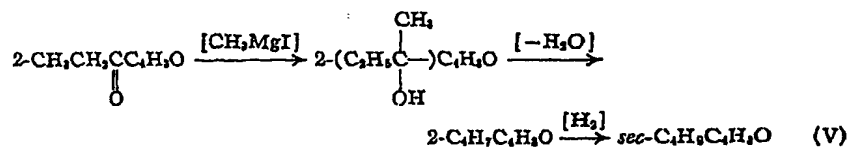
This mercurial as well as the butylfuran from which it was prepared were shown to be unlike the other three possible 5-butyl-2-furylmercuric chlorides and the corresponding 2-butylfurans. The *n*-butyl- and isobutylfurans were synthesized as follows



The following reactions illustrate the synthesis of *sec*-butylfuran

(5) Gilman and Wright, *Chem. Rev.*, **11**, 380 (1982).

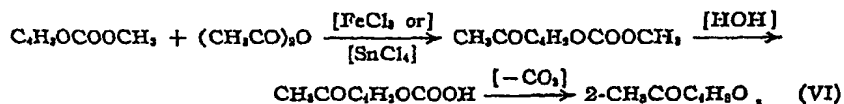
(6) Asubina and Murayama, *Arch. Pharm.*, 252, 425 (1914).



This sequence of reactions is related to that used recently⁷ for the preparation of 2-isopropylfuran $\text{C}_4\text{H}_5\text{OCOOC}_2\text{H}_5 \xrightarrow{[\text{CH}_3\text{MgI}]} \text{C}_4\text{H}_5\text{OC(CH}_3\text{)}_2\text{OH} \xrightarrow{[-\text{H}_2\text{O}]} \text{C}_4\text{H}_5\text{OC(CH}_3\text{)=CH}_2 \xrightarrow{[\text{H}_2]} \text{C}_4\text{H}_5\text{OCH(CH}_3\text{)}_2$. Our isopropylfuran is identical with this compound, and thus gives added support to the generalization⁸ that nuclear substitution occurs in an α -position if one be available.

Methyl chloride gave a dithio ester, as a consequence of interaction with the carbon disulfide;⁸ ethyl chloride and ethyl bromide apparently undergo a reaction like that observed with methyl chloride; both *n*-propyl and isopropyl chloride gave the same isopropyl derivative [methyl 5-isopropyl-2-furoate], so that smooth alkylation of methyl furoate really starts with the propyl halides; and the amyl and hexyl derivatives, prepared from *n*-amyl chloride and *n*-hexyl bromide, probably are branched chain types by analogy with the formation of *tert*-butylfuran from each of the four isomeric butyl halides.

The structures of the acylation products of methyl furoate were established as follows, using acetic anhydride as a type



The chief problem in determining the constitution of a monoacylated nuclear substituted product of a di- α -substituted furan having like substituents concerns the integrity of the furan nucleus. The nucleus is not cleaved significantly in a Friedel-Crafts reaction. This was established in the case of the acetylated 2,5-dimethylfuran by preparing the same compound from 2,5-dimethylfurylmercuric chloride and acetyl chloride. The resulting 2,5-dimethyl-3-furyl methyl ketone was prepared earlier by the condensation of succinic acid and acetic anhydride with zinc chloride.⁹

An anomalous reaction takes place between 2-furfural and isopropyl chloride. The product is not 5-isopropyl-2-furfural, but appears to be a related dihydrofuran or possibly a compound formed by nuclear cleavage.

Experimental Part

2-Furyl Phenyl Ketone and *tert*-Butyl Chloride.—Eight grams (0.05 mole) of 2-furyl

(7) Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, 15, 1118 (1932).

(8) Jorg, *Ber.*, 60, 1466 (1927).

(9) Magnanini and Bentivoglio, *Gazz. chim. Ital.*, 24, I, 435 (1904).

phenyl ketone in carbon disulfide were brought into reaction with *tert*-butyl chloride and aluminum chloride under the conditions described later [see "Alkylation of Methyl 2-Furoate"], with the exception that no ice-bath was used. The resulting 5-*tert*-butyl-2-furyl phenyl ketone (30% yield) is unusually stable: b. p. 180–182° (20 mm.) and 187–189° (22 mm.); d_{25}^{25} 1.065; n_D^{25} 1.5865.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.94; H, 7.06. Found: C, 79.06; H, 7.54.

The same compound was obtained in a 70% yield by condensing 5-*tert*-butyl-2-furoyl chloride (0.1 mole), aluminum chloride (0.1 mole) and 100 cc. of benzene.

The 5-*tert*-butyl-2-furoyl chloride was obtained (51% yield) by refluxing 5-*tert*-butyl-2-furoic acid with thionyl chloride; b. p. 220°; d_{25}^{25} 1.108; n_D^{25} 1.5091.

Anal. Calcd. for $C_{15}H_{16}O_2Cl$: Cl, 19.03. Found: Cl, 19.37.

2-Furfural and Isopropyl Chloride.—In an experiment with 0.5 mole of furfural, 0.5 mole of isopropyl chloride, and 0.8 mole of aluminum chloride in carbon disulfide no external cooling was applied. There was a marked evolution of hydrogen chloride, and but very little charring was noted. Subsequent to hydrolysis of the reaction mixture, the carbon disulfide layer was washed first with water and then with sodium acetate. Then 200 cc. of a saturated solution of sodium acetate was added, and the resulting aldehyde steam distilled. This aqueous distillate was extracted with the carbon disulfide which first distilled over, washed with sodium bicarbonate, dried over sodium sulfate, and the aldehyde, after removing carbon disulfide, was distilled under reduced pressure.

The yield was 8 g. of aldehyde distilling at 101–103° (21 mm.); d_{25}^{25} 1.023; n_D^{25} 1.5041. The constitution of this aldehyde has not yet been established, but it appears to be a dihydrofuran derivative.

Anal. Calcd. for $C_5H_8O_2$: C, 68.52; H, 8.84. Found: C, 69.49; H, 8.38.

The aldehyde is relatively unstable and darkens on atmospheric exposure. When oxidized by alkaline silver oxide it gives a carboxylic acid which is unlike 5-isopropyl-2-furoic acid.⁷ This new acid, which may be a dihydro-isopropylfuroic acid or a ring scission product, melts at 76–77° when crystallized from 40% ethyl alcohol. In an orienting experiment the supposed dihydroisopropylfuroic acid was heated with phosphorus pentachloride to remove two hydrogens and give the known 5-isopropyl-2-furoic acid⁷; however, the original acid was recovered after alkaline hydrolysis. *Neutralization equivalent.* Calcd., 156; found, 155.

Anal. Calcd. for $C_8H_{10}O_3$: C, 61.49; H, 7.75. Found: C, 61.71; H, 7.45.

The semicarbazone of the aldehyde melts at 174–176° when crystallized from 30% alcohol, and its analysis agrees for a dihydro derivative.

Anal. Calcd. for $C_8H_{10}O_2N_2$: C, 54.79; H, 7.66. Found: C, 54.85; H, 7.42.

The unknown aldehyde was condensed with sodium acetate and acetic anhydride to give a 40% yield of an acid which analyzes for a dihydroisopropylfurylacrylic acid. This acid melts at 102–103° when crystallized from water and alcohol. *Neutralization equivalent.* Calcd., 182.1; found, 180.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 65.89; H, 7.74. Found: C, 65.93 and 65.93; H, 7.75 and 7.66.

Furan and Acid Chlorides.—To 26.8 g. (0.2 mole) of aluminum chloride in 250 cc. of carbon disulfide contained in a three-necked flask provided with a mechanical stirrer was added 0.2 mole of the acid chloride. The flask and contents were then chilled with an ice-bath. Furan (0.2 mole), prepared in accordance with recent directions,¹⁰ contained in 50 cc. of carbon disulfide was added dropwise over a twenty-five minute period;

(10) Gilman and Lousinian, *Rec. trav. chim.*, **52**, 156 (1933).

the mixture turned dark brown, and after about one-third of the furan had been added copious quantities of hydrogen chloride were evolved. Stirring was continued for fifteen minutes in the ice-bath, and then for ten minutes at room temp., after which the mixture was poured upon 300 g. of cracked ice, and steam distilled; the distillate was made alkaline with potassium hydroxide, extracted with ether, dried over sodium sulfate, and the alkyl 2-furyl ketone distilled under reduced pressure. The data are given in Table I.

TABLE I
ALKYL 2-FURYL KETONES FROM FURAN AND ACID CHLORIDES

Alkyl 2-furyl- ketone	RCOCl used	Yield, %	B. p. (mm.), °C.	d_{44}^{25}	n_D^{25}
1 Ethyl	<i>n</i> -Propionyl	36.3	78-80 (17) m. 27-28°
2 <i>n</i> -Propyl	<i>n</i> -Butyryl	51.8	95-97 (10)	1.041	1.4922
3 Isopropyl	Isobutyryl	45.3	80-87 (18)	1.032	1.4888
4 <i>n</i> -Butyl	<i>n</i> -Valeryl	23	108-109 (18)	1.012	1.4900
5 <i>n</i> -Amyl	<i>n</i> -Caproyl	39	116-119 (16)	0.0054	1.4864

Analyses, %				Semicarbazone and analyses			
Calcd.		Found		Calcd.		Found	
C	H	C	H	M. p., °C.	Carbon	Hydrogen	
1	67.71	6.50	67.65	6.66	188-190	(a)	(a)
2	69.52	7.30	70.02	7.40	190	(a)	(a)
3	69.52	7.30	69.45	7.63
4	71.01	7.96	71.32	8.15	158-159	57.22	57.22
5	72.24	8.49	71.77	8.76	110-112	54.68	54.97

TABLE II
ALKYLATION OF METHYL 2-FUROATE

Methyl 5-alkyl 2-furoate		Alkyl halide used	Yield, %	B. p. (mm.), °C.	d_{44}^{25}	n_D^{25}
1	5-Isopropyl-	<i>n</i> -Propyl chloride ^b	48	110-112 (20)	1.070	1.4851
2	5- <i>tert</i> -Butyl-	<i>n</i> -Butyl chloride ^c	45	110-114 (15)	1.037	1.4702
3	5-Amyl-	<i>n</i> -Amyl chloride	31	112-116 (13)	1.032	1.4804
4	5-Hexyl-	<i>n</i> -Hexyl bromide	57.1	132-136 (10)	1.016	1.4814

Analyses, %				5-Alkyl-2-furoic acid and analyses					
Calcd.		Found		M. p., °C.	Calcd.		Found		
C	H	C	H		C	H	C	H	
1	64.24	7.20	63.87	7.36	65-66	62.29	6.54	62.45	6.44
2	65.90	7.74	66.20	7.91	104-105	64.24	7.20	64.51	7.40
3	67.34	8.16	67.10	8.21	69.70	65.90	7.44	66.3	7.95
4	68.34	8.63	68.45	8.51	36-37	67.34	8.16	67.1	7.99

^a These semicarbazones were prepared and analyzed by Asahina and Murayama.¹

^b The yield of methyl 5-isopropyl-2-furoate from isopropyl chloride was 42%. ^c From 12.6 g. (0.1 mole) of methyl furoate, 0.1 mole of *tert*-butyl chloride, 0.12 mole of ferric chloride in place of aluminum chloride and 100 cc. of carbon disulfide there was isolated but two fractions: one of these (8 g.) was recovered methyl furoate and the other a 41.3% yield of methyl 5-*tert*-butyl-2-furoate. The yield of methyl 5-*tert*-butyl-2-furoate from isobutyl bromide was 86%; from *sec*-butyl bromide, 1.6%; and from *tert*-butyl bromide, 46%.

The several ketones were also prepared by interaction of 2-furyl-mercuric chloride and the appropriate acid chloride, in accordance with recent directions.¹¹ The ketones

(11) Gilman and Wright, THIS JOURNAL, 55, 3302 (1933).

prepared by these two methods were identical, as established by mixed melting point determinations of the semicarbazones. The yields of alkyl 2-furyl ketones prepared from 2-furylmercuric chloride were as follows: ethyl, 24.2%; *n*-propyl, 18.1%; isopropyl, 14.5%; and *n*-amyl, 18%.

In accordance with Steinkopf's¹² directions for the preparation of 5-ethyl-2-thienyl ethyl ketone from ethylthiophene, propionyl chloride and phosphorus pentoxide, a reaction was attempted between furan, ethyl chlorocarbonate and phosphorus pentoxide. The furan was recovered practically quantitatively.

The difficulty in *alkylating* furan with *n*-butyl chloride, aluminum chloride and carbon disulfide or furan itself as a medium may be due in part to a coating which formed on the aluminum chloride.

Alkylation of Methyl 2-Furoate.—In these experiments 0.1 mole of methyl furoate and 0.1 mole of alkyl halide was added dropwise over a twenty-five minute period to 0.1–0.2 mole of aluminum chloride and 200 cc. of carbon disulfide contained in a three-necked flask provided with a mechanical stirrer and cooled by an ice-bath. A dark, viscous oil separated in each case leaving a clear supernatant liquid, and hydrogen chloride was evolved promptly with the lower halides but more slowly with the higher ones. When addition was complete, the ice-bath was removed and the mixture allowed to stand for twenty-four hours. Because the evolution of hydrogen halide is very slow with *n*-hexyl bromide, the ice-bath was removed directly after admixing the reactants. The reaction product was poured upon 500 g. of cracked ice with *vigorous* stirring to prevent extreme local heating, the solvent separated, and the aqueous layer extracted three times with 200-cc. portions of ether. The ether and carbon disulfide solutions were combined, washed with 200 cc. of water and then with 200 cc. of a saturated sodium bicarbonate solution, dried over sodium sulfate, and the heavy residual liquid (after removing the solvents) was fractionated in a Claisen flask with indentations. It was found desirable to fractionate at least three times in order to obtain a product which on hydrolysis would yield a solid acid; otherwise, oily acids are obtained which are very difficult to crystallize. In view of the difficulty of fractionation it appears altogether reasonable to conclude that isomeric 2-butyl esters were formed.

Hydrolysis was effected by heating 10 g. of the ester at 80° with a 20% solution of alcoholic potassium hydroxide for ten minutes. The mixture was then poured into 100 g. of cracked ice in 200 cc. of water, and acidified slowly by the addition, with stirring, of 50% iced sulfuric acid. Solution in cold dilute potassium hydroxide and reprecipitation with cold sulfuric acid is sometimes desirable. Crystallization is effected from an alcohol–water mixture. The yields on hydrolysis are in excess of 75%. Unnecessary heating should be avoided to prevent the precipitation of the acids as oils. The data are given in Table II.

The best method for the preparation of 5-*tert*-butyl-2-furoic acid is probably that one involving the use of isobutyl bromide. The actual reaction is completed in three hours (and the entire preparation in five hours); but one fraction is obtained and this distills at 110–116° (20 mm.) to give a 77% yield. Redistillation gives a 88% yield of ester distilling at 112–114° (20 mm.).

In the reaction with methyl chloride, the gas was bubbled into a mixture obtained by adding 63 g. or 0.5 mole of methyl furoate to 1 mole of aluminum chloride in 300 cc. of carbon disulfide. The reaction product yielded 35 g. of the original methyl furoate and 25 g. of a red viscous oil which when finally crystallized from an alcohol–water mixture melted at 102–103°. This experiment was checked. However, when petroleum ether (b. p. 30–60°) was used as a medium in place of carbon disulfide, only methyl furoate was isolated (85% recovery). The deep red compound is uncommonly stable under ordinary conditions, and the color was not discharged by heating for one

(12) Steinkopf, *Ann.*, 430, 105 (1923).